The predictive value of albuminuria for renal and nonrenal natural death over 14 years follow up in a remote Aboriginal community

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Abstract

Background. Australian Aboriginal people living in remote regions have extraordinary higher rates of mortality compared to other Australian ethnicities. Albuminuria marks the underlying renal disease. This study assessed the predictive value of albuminuria for nonrenal and renal death in a remote Australian Aboriginal community over follow-up of more than 14 years.

Methods. From 1992-1997, 85% of community members participated in a health screen, which included measurement of urine albumin/creatinine (ACR) levels. Deaths and dialysis starts were recorded until 30 November 2010. Rates of natural nonrenal and renal death were assessed over a mean of 14 years in the 956 participants aged 18 years and over at baseline, and mortality associated with baseline levels of albuminuria (ACR $\geq$2.7 mg/mmol) was estimated.

Results. There were 203 natural deaths; 70 were renal deaths and 133 were nonrenal deaths, including 60 CVD deaths. Higher baseline ACR predicted all categories of natural death, with no apparent lower threshold for effect. Baseline ACR $\geq$2.7 mg/mmol predicted a 3.3-fold increase in all natural death, a 2-fold increase in nonrenal death, and 1.7-fold increase in CVD deaths, after adjustment for other factors. Eighty-nine percent (62 out of 70) of renal deaths occurred in those with ACR $\geq$34 at baseline, with a 24-fold increase in risk. Albuminuria **(**ACR $\geq$2.7 mg/mmol**)** contributed to 66% of risk for all natural death over the interval.

Conclusions. Albuminuria was still a remarkable predictor for all –causes natural death over an average 14 years follow up interval in this Aboriginal community.

Abstract word count: 247

Key words: Aboriginal people; ACR; albuminuria; nonrenal death; renal death.

Short summary: We assessed the predictive value of albuminuria for mortality in a remote Australian Aboriginal community over follow-up of more than 14 years. Albuminuria was still a remarkable predictor for natural mortality over such a long-term period.

Introduction

Australian Aboriginal people, especially those living in remote regions, have higher rates of all–cause mortality, of cardiovascular deaths and of end-stage renal disease (ESRD), [1,2] compared to other Australian ethnicities. The disparities are worse for younger age groups. Adult Aborigines in the Northern Territory have mortality rates two to four times higher than non-Aboriginal Australians, while the death rates of 25 to 44 years olds are increased approximately 15–fold.[3]

The incidence of ESRD among Aborigines living in remote regions is increased up to 30 times the national incidence for all Australians.[4,5] The high number of renal deaths and nonrenal deaths for Aboriginal people are by no means explained solely by diabetes and its co-morbidities. [6, 7] Albuminuria marks the underlying renal disease. In a study of one high-risk community, we showed that albuminuria, which was pervasive, not only marked all the future risk for renal deaths, but also predicted cardiovascular and non-renal non-cardiovascular deaths. [8-10] In that study, 825 adults, of a mean age of 33.6 years, were followed for a total of 4778 person years and average of 5.8 years; they experienced 64 natural death endpoints: of which 16 were renal and 36 were cardiovascular. Albuminuria (ACR 3.4 mg/mmol and above) was estimated to contribute to all the renal deaths and 75% of the risk for nonrenal natural deaths over that interval. [1] Studies in other populations and ethnic groups have also documented the association of albuminuria with non-renal death particularly CVD mortality as well with renal disease and renal death. [6, 10, 11] In one study of people aged 55 years and over, the exacerbation of risk for CVD started at a very low level of ACR. [12]A collaborative meta-analysis indicated that ACR 1.1 mg/mmol or more is an independent predictor of mortality risk in the general population. [13]

A screening and treatment program for renal disease and hypertension was started in this community in Nov 1995 and was conducted with some vigour through mid 1999. It was associated with significant reduction of mortality in treated persons compared with historical controls matched for disease severity. [8] With a change in health service administration the intervention faltered for a time, but in recent years has been taken up again, with protocols of systematic surveillance and treatment now embedded within primary care, although resources limit their optimal application. In a repeat community screen from 2004-2006, 30.4% adults

overall, and 52% of those of 50 years and over had prescriptions for antihypertensive agents (usually perindopril) and 18.1% overall, and 34% of those age 50 years and over had prescriptions for hypoglycaemic agents. [14]This was the first Aboriginal community in which the effects of angiotensin converting enzyme inhibition in delaying renal and nonrenal deaths in people with albuminuria and hypertension were demonstrated. [8, 15] This has subsequently become standard practice in all remote Aboriginal health services, and has contributed to the reduction in Indigenous death rates in the Northern Territory [21] and nation-wide.[5,16]

We now describe terminal events in this cohort through a follow up of up to over 14 years in order to: define whether albuminuria remains a significant predictor of mortality over the longer period;

- examine possible relationships with ACR over a continuum; and probe for the predictive value of ACR below traditional cut-off point for microalbuminuria.

Subjects and methods

Subjects were adults in a remote Aboriginal community who participated in the baseline health survey between 1992 and 1997 at ages ranging from 18-76 years. The profiles of this community have been described previously [6] . Minimum data for inclusion of 956 subjects were age, sex and urine ACR. The sample size was somewhat smaller when covariates such as weight, height, blood pressure, lipoprotein and blood glucose were included in analyses.

All natural deaths were documented until 30 November 2010, as recorded in community and hospital records. All death files were confirmed in the local Catholic Church Burial Records. Natural deaths were categorized by their primary or underlying cause, into renal, non-renal natural death and cardiovascular death, as described previously. [17] Renal death refers to participants who started dialysis for ESRD or who died with terminal renal failure without dialysis. The survival time of people who died of nonnatural deaths, which included acute intoxications, accidents, drowning, suicide and homicide, was documented: they were censored from the analysis at time of death, and their deaths were not included in this analysis.

Height, weight, blood pressure and levels of glycemia were measured using standard procedures. Some diagnostic criteria used in this study were as follows:

- Diabetes: known to be diabetic before the survey and/or with fasting glucose ≥7.0 mmol/L) (≥ 126.1 mg/dl) or 2-hr glucose or random glucose level ≥ 11.1 mmol/L (200 mg/dl) at testing.
- Obesity : BMI ≥ 30 kg/m^2
- Hypertension: SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg

Urine albumin concentrations were measured simultaneously by both nephelometric and HPLC techniques on baseline random urine samples after retrieval from -70^{o}C storage. When examined over a Z score continuum of their values, they were identical in defining clinical profiles and predicting death.[20] Results here are based on ACR levels derived from albumin measured by immunonephelometry (Beckman Instruments, Brea, CA), and from urinary creatinine concentration measured using the modified kinetic Jaffe reaction (Olympus AU600 Autoanalyzer; inter-assay CV 2%). As the median value of ACR of this cohort was 2.7 mg/mmol, which is lower than the conventional microalbuminuria cut-off point, albuminuria was arbitrarily defined as urine ACR≥2.7mg/mmol in this study, while the conventional threshold of ACR ≥34 mg/mol was defined as overt proteinuria.

Quartiles of ACR level and log-transformed (log base 2) ACR were applied in the analyses. Baseline characteristics across progressive quartiles of ACR were compared. Cox regression analyses were employed to calculate hazard ratios (95% CI) of all natural death, renal, nonrenal and CVD death predicted by ACR, and to allow adjustment for age, sex and other covariates. The Kaplan-Meier method was used to estimate fractional survivals according to different baseline ACR levels. The population attributable fraction (PAF) of mortality predicted by the presence of ACR≥2.7 (mg/mmol) at baseline was calculated using poisson regression adjusted for age, sex and time of follow up year. All analyses were undertaken using Stata 11.1 (Stata Corp. Stata Statistical Software: Release 11.1, College Station. TX: StataCorp LP, 2009). Statistical significance was defined at the level of $p < 0.05$ (two-tailed).

This study was approved by the Ethics Committee of the Menzies School of Health Research and Territory Health Services and The Behavioural and Social Science Ethical Review Committee of the University of Queensland.

Results

Those 956 participants were followed for a total of 13,714 years, a range of 0 to 18 years, and a median and mean of 16 and 14 years respectively. ACR ranged 0-675.5 (mg/mmol) with median value of 2.7 (mg/mmol). Their characteristics by baseline quartiles of ACR are shown in Table1. Age was progressively higher with higher ACR quartiles, and levels of cholesterol and triglycerides, and the percentage with obesity, hypertension and diabetes was also higher, either across quartiles on a continuum or with level above the ACR median. Those in the highest quartile were more often female.

A total of 203 natural deaths were documented while 37 people died of misadventure (nonnatural deaths).The natural deaths included 70 renal deaths and 133 nonrenal deaths of which 60 were CVD deaths. Table 2 shows deaths by gender: numbers and rates of renal deaths were more common in females, but there was no gender difference in other categories of death.

Table 3 shows the numbers and rates of natural death by quartile of baseline ACR level. The incidence of all natural death, non-renal and CVD death rose significantly with increasing ACR quartiles. However all renal deaths were confined to people in quartiles 3 and 4 of baseline ACR levels, i.e., ACR ≥ 2.7 mg/mmol. Figures 1A, 1B and 1C show the Kaplan-Meier survival curves for all natural death, for renal and for nonrenal death by baseline ACR quartiles. After 14 years, only 51.4% of people in the highest baseline ACR quartile had avoided all natural death: 70.3% had avoided renal death and 73.1% had avoided nonrenal deaths. The survival curve of renal death for people within the category of the highest ACR quartile was significantly different from people in lower ACR quartile, and so was for nonrenal death.

Table 4 lists HRs (95% CI) of different end-points according to quartiles of baseline ACR and log-transformed (base 2) ACR. The risks of all natural death and of non-renal death rose with increasing ACR quartiles, and with each doubling of ACR, with similar levels of risk exacerbation for females and males. For example, the HRs (95%CI) of log-transformed (base 2) ACR for all natural death were 1.4 (1.3-1.6) for females, 1.3 (1.1-1.4) for males; and the HRs for non-renal death were 1.2 (1.0-1.3) for females and 1.1 (1.0-1.3) for males. Compared to those with the first ACR quartile, the risks of CVD death were significantly and comparably

raised in those with ACR in the second and third quartiles, and strikingly elevated in those in the highest ACR quartiles. The trends persisted with adjustment for age, sex and other factors, including blood pressures and glucose levels (Table 4).

Figure 2 shows predicted renal and nonrenal death by log-transformed (based 2) ACR for people aged 18 years and over. The statistical significance between two curves has been calculated by comparing their ROC curves. It indicated that the ROC curve for renal death predicted by ACR is significantly larger than for non-renal death. The rate of increase of predictions of non-renal death rate speeds up at ACR level less than 3.4 mg/mmol, while the threshold for renal death was at a higher ACR level (figure 2). Table 5 shows people with ACR ≥2.7 (mg/mmol) (the group median) predicted 3.3-fold increase in all natural death, and 2.2-fold and 1.9-fold increases in non-renal deaths and CVD deaths respectively relative to the people with ACR <2.7 after adjusting for sex and age. As no renal deaths occurred in those with ACR <2.7/mg/mmol) (Table 5), the HR of ACR ≥2.7 vs.<2.7 could not be calculated (Table 5). However, eighty-nine percent (62 out of 70) of renal deaths occurred in those with ACR ≥34 at baseline, with HR (95%CI) of 23.8 (8.0-71.2) for females and 23.7 (4.1-135.0) for males after adjustment for a number of risk factors . It also shows that the population attributable fraction of natural deaths associated with ACR levels at or above the median value of 2.7 mg/mmol was 66% for all natural death, 45% for nonrenal deaths and 34% for CVD death (Table 5).

When analysed around the "traditional" microalbuminuria cut-off of ACR ≥ 3.4 mg/mmol, the PAFs were 64% for all natural death, 41% for nonrenal death and 32% for CVD death. These compare with those of 84%, 65% and 75% those categories of deaths calculated by Hoy et al in the first five years of the observation in people before systematic treatment was initiated. [6]

Discussion

In this community, albuminuria (ACR≥2.7mg/mmol) predicted nonrenal death while overt proteinuria (ACR ≥34 mg/mmol) predicted renal death over an average 14 years follow up (median follow up of 16 years). This confirms our previous observation of the predictive value of albuminuria for natural death over a much shorter interval in people who were followed without or before the introduction of systematic treatment.[8] The relationship still applies, over

almost 3-fold increase in average duration of follow up, almost three times the number of person years follow up, and more than 3 times the number of deaths. Among these deaths, the number of renal deaths was increased more than 3-fold, and of CVD deaths more than doubled. Despite advancing age, the mortality of those without pathologic albuminuria at baseline remains small, and that those with the highest baseline levels continue to do worse even after 10-15 years.

The relationships also remained strong against a changing background of events, which include a fluctuating level of surveillance and treatment, and against a background of falling mortality rates overall. Falling mortality rates, which were first detected after introduction of systematic treatment, are now evident from overall community deaths and census data, and were echoed in falling mortality rates in remote Australian Aboriginal people more generally (report in preparation),

To our knowledge this is the longest follow up study of the predictive values of albuminuria over natural death although many population-based studies in this subject have been published in last decades.[13,18-26] For example, Drury et al reported that reduced eGFR and albuminuria are independent risk factors for CVD events and mortality rate in a 5-year follow up diabetic cohort. [22] In a 12.9- year follow-up for the cohort of 1,113 elderly men, urinary albumin excretion rate (UAER) and eGFR increased risk for CVD death. [24]

The population attributable fractions calculations suggest that 66% of all natural deaths including 100% of renal deaths and 45% of nonrenal death would have been avoided if baseline ACR levels had been uniformly less than the population median of 2.7 mg/mmol. Alternatively, with all baseline levels <3.4 mg/mmol, the “traditional” microalbuminuria threshold, the avoided proportions would have been 64% for all natural death, 100% for renal death and 41% for nonrenal death respectively.

The substantial reduction in population attributable fractions of ACR ≥3.4 for all natural death and nonrenal death over the longer follow up in relation to that in our first report is probably due to culling of people at highest risk for death from the cohort in the early years, as well as mitigation of outcomes due to more systematic treatment of those with disease. This should

also have improved the outcomes in people who were “normal” at baseline, who subsequently developed overt albuminuria or hypertension, if they were detected and treated**.** Despite these considerations, albuminuria remained a powerful predictor of all-cause natural death over a 14-year period. These provide powerful arguments for unflagging efforts to prevent the development of pathologic levels of albuminuria and to reduce its progression.

In our study the predictions of renal death by baseline ACR levels were incontrovertible, but with a threshold level of baseline ACR that was clearly already abnormal (i.e., ACR≥2.7 mg/mmol). However, it also showed prediction of nonrenal death by baseline ACR levels starting below the traditional microalbuminuria cut-off (3.4mg/mmol). This supports the 2001 report of Gerstein et al in a group subjects aged 55 years or more, with or without diabetes in the context of cardiovascular risk prediction. [12] The potential explanations of these important associations remain speculative.

In this study, estimated GFR (MDRD formula, without adjustment for race) was also a significant predictor for renal deaths in the presence of other factors, including ACR. However, the predictive value of the terminal outcome by ACR was not much affected by adding GFR in the modelling. Previous reports also suggested that the predictive value of microalbuminuria on mortality is independent of eGFR, [27] and albuminuria and eGFR were multiplicatively associated with all –cause mortality without evidence for interaction. [13, 21, 26]

The rates of renal death in this Aboriginal cohort are astounding compared with those in Western populations. Females had a significantly higher renal death rate than males, which is also seen in other remote Aboriginal populations. [14] This is consistent with the higher prevalence of albuminuria in females than in males, which in turn might be related to their lower birthweights and higher rates of diabetes, as well as their failure to show usual female-related relative protection from childhood poststreptococcal glomerulonephritis, [6, 14, 28, 29]

Strengths of this study are more than 80% community participation in the baseline screen, the excellent ascertainment of outcomes and the long duration of follow up. Potential weaknesses include the fact that only one baseline random urine sample was taken and that

ACR was not confirmed with a morning urine sample, and the necessary "lumping" of categories of death into mutually exclusive categories by primary or underlying cause, whereas most natural deaths actually had more than one underlying morbid or contribution condition. However, demonstration of the relationship of albuminuria to the distinct and accurate category of all-cause natural death is clear. Furthermore, the main predictions are unchanged when death are grouped by both underlying and associated causes. The changing background of underlying health profiles and of disease management in the follow up period poses an additional challenge to mechanistic interpretation, but it represents the real world of health service delivery, against which the phenomenon described here remains very powerful. Finally, nearly one third of the variances for all natural death remain unexplained by these simplistic models. We anticipate that these findings will apply to other remote Aboriginal communities with similar renal failure and mortality profiles. [5] However they need to be tested in the context of less remote-living Indigenous Australians, who have lower rates of both nonrenal and renal death.

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Disclosure

All the authors declared no competing interests

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Table 1 Characteristics of participants aged 18 years and over with ACR quartiles

Characteristics	ACR quartile 1 (ACR range 0-0.6)	ACR quartile 2 (ACR range 0.7-2.7)	ACR quartile 3 (ACR range 2.7-19.5)	ACR quartile 4 (ACR range 19.6-675.5)	p value
Female %	40.8	50.6	46.8	59.2	0.001
Age (year)	30.2 (10.4)	32.3 (11.5)	35.0 (11.8)	42.0 (12.1)	<0.001
Total cholesterol (mmol/L)	4.37 (1.01)	4.51 (1.01)	4.71 (1.05)	5.21 (1.28)	<0.001
HDL cholesterol (mmol/L)	1.15 (0.33)	1.14 (0.28)	1.10 (0.25)	1.06 (0.23)	0.0064
Triglyceride (mmol/L)	1.64 (1.29)	1.84 (1.25)	2.14 (1.24)	3.12 (2.68)	<0.001
Obesity%	8.4 (4.9-12.0)	7.6 (4.2-11.0)	16.2 (11.4-20.9)	24.6 (19.0-30.1)	<0.001
Hypertension%	13.5 (9.1-17.9)	14.7 (10.1-19.3)	23.9 (18.4-29.4)	41.7 (35.4-48.1)	<0.001
Diabetes %	2.5 (0.5-4.5)	7.1 (3.8-10.3)	10.6 (6.7-14.5)	31.8 (25.9-37.7)	<0.001

Notes: data were mean (SD) for continuous variables and percentage (95% CI) for categorical variables

Table 2 Natural death by sex for Tiwi people aged 18 years and over

	Men	Women	All	P value
Number of participants	485	471	956	
Follow-up years	6,930	6,785	13,714	
All natural death				
Number	100	103	203	
Incidence	14.4 (11.8-17.5)	15.2 (12.4-18.4)	14.8 (12.8-17.0)	0.7159
Renal death				
Number	26	44	70	
Incidence	3.8 (2.5-5.5)	6.5 (4.7-8.7)	5.1 (4.0-6.4)	0.0247
Non-renal death				
Number	74	59	133	
Incidence	10.7 (8.4-13.4)	8.7 (6.6-11.2)	9.7 (8.1-11.5)	0.2362
CVD death				
Number	35	25	60	
Incidence	5.1 (3.5-7.0)	3.7 (2.4-5.4)	4.4 (3.3-5.6)	0.2256

Notes: p value refers to comparison between men and women; Incidence refers to death per 1,000 person years (95% CI);

Table 3 Natural death by ACR quartile for Tiwi people aged 18 years and over

	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P trend
ACR range (mg/mmol)	0-0.6	0.7-2.7	2.72-19.6	20.2-675.5	
Number of participants	240	241	236	239	
Follow-up years	3,766	3,736	3,465	2,749	
All natural death					
Number	11	25	42	125	
Incidence	2.9 (1.5-5.2)	6.7 (4.3-9.9)	12.1 (8.7-16.3)	45.5 (38.0-53.9)	<0.001
Renal death					
Number	0	0	5	65	
Incidence			1.4 (0.5-3.4)	23.6 (18.3-33.3)	<0.001
Non-renal death					
Number	11	25	37	60	
Incidence	2.9 (1.5-5.2)	6.7 (4.3-9.9)	10.7 (7.5-14.7)	21.8 (16.7-28.1)	<0.001
CVD death					
Number	4	15	11	30	
Incidence	1.1 (0.3-2.7)	4.0 (2.2-6.6)	3.2 (1.6-5.7)	10.9 (7.4-15.5)	<0.001

Notes: Incidence as per 1,000 person years (95% CI);

Table 4 Hazard ratios (95% CI) of outcomes by ACR quartile and log-transformed (base 2) ACR

	ACR quartiles					
	1	2	3	4	P trend	Log 2ACR
ACR range (mg/mmol)	0-0.6	0.7-2.7	2.72-19.6	20.2-675.5		0-675.5
All natural death						
Crude HR (95% CI)	1.0	2.3 (1.1-4.7)	4.2 (2.1-8.1)	15.7 (8.5-29.1)	<0.001	1.4 (1.4-1.5)
HR1 (95% CI)	1.0	2.0 (1.0-4.2)	3.3 (1.7-6.5)	9.5 (5.1-17.6)	<0.001	1.3 (1.3-1.4)
HR2 (95% CI)	1.0	1.5 (0.7-3.3)	2.6 (1.3-5.4)	6.2 (3.1-12.4)	<0.001	1.3 (1.2-1.4)
HR3 (95% CI)	1.0	1.7 (0.7-3.9).	3.2 (1.5-7.0)	7.8 (3.7-16.6)	<0.001	1.4 (1.3-1.5)
HR4 (95% CI)	1.0	1.4 (0.6-3.0)	2.5 (1.2-5.1)	5.9 (3.0-11.9)	<0.001	1.3 (1.2-1.4)
HR5 (95% CI)	1.0	1.0 (0.4-2.5)	2.2 (1.0-4.7)	5.1 (2.4-10.6)	<0.001	1.3 (1.2-1.4)
Renal death*						
Crude HR (95% CI)						2.4 (2.0-2.8)
HR1 (95% CI)						2.4 (2.0-2.8)
HR2 (95% CI)						2.7 (2.1-3.4)
HR3 (95% CI)						2.8 (2.3-3.6)
HR4 (95% CI)						2.7 (2.1-3.4)
HR5 (95% CI)						3.0 (2.2-4.0)
Non-renal death						
Crude HR(95% CI)	1.0	2.3 (1.1-4.7)	3.7 (1.9-7.2)	7.5 (3.9-14.2)	<0.001	1.2 (1.2-1.3)
HR1 (95% CI)	1.0	2.0 (1.0-4.1)	2.8 (1.4-5.5)	4.0 (2.1-7.8)	<0.001	1.1 (1.1-1.2)
HR2 (95% CI)	1.0	1.5 (0.7-3.2)	2.3 (1.1-4.7)	2.9 (1.4-6.1)	0.001	1.1 (1.0-1.2)
HR3 (95% CI)	1.0	1.6 (0.7-3.8)	2.7 (1.2-6.0)	3.3 (1.5-7.4)	0.001	1.1 (1.1-1.3)
HR4 (95% CI)	1.0	1.2 (0.5-2.7)	1.9 (0.9-3.9)	2.4 (1.1-5.2)	0.006	1.1 (1.0-1.2)
HR5 (95% CI)	1.0	1.1 (0.5-2.9)	1.9 (0.9-4.2)	2.2 (1.0-4.9)	0.023	1.1 (1.0-2.2)
CVD death						
Crude HR (95% CI)	1.0	3.8 (1.3-11.4)	3.0 (1.0-9.4)	10.1 (3.5-28.7)	<0.001	1.2 (1.1-1.4)
HR1 (95% CI)	1.0	3.5 (1.1-10.4)	2.4 (0.8-7.6)	6.1 (2.1-17.7)	0.001	1.2 (1.1-1.3)
HR2 (95% CI)	1.0	2.5 (0.8-8.0)	1.9 (0.6-6.0)	3.7 (1.2-11.5)	0.033	1.1 (1.0-1.3)

HR3 (95% CI)	1.0	3.4 (0.9-12.5)	2.6 (0.7-9.7)	4.8 (1.3-17.0)	0.023	1.1 (1.0-1.3)
HR4 (95% CI)	1.0	2.2 (0.7-7.0)	1.6 (0.5-5.1)	3.2 (10-10.0)	0.067	1.1 (1.0-1.3)
HR5 (95% CI)	1.0	2.1 (0.6-7.2)	1.5 (0.5-5.1)	2.7 (0.8-8.6)	0.135	1.1 (1.0-1.3)

Notes: * the HR of renal death by log-transformed ACR; HR 1 adjusted for sex and age; HR 2 adjusted for sex, age, diabetes, hypertension, obesity, total cholesterol, HDL and triglycerides ; HR 3 adjusted for sex, age, systolic blood pressure, plasma glucose, obesity, total cholesterol, HDL and triglycerides; HR 4 adjusted for sex, age, diabetes, hypertension, obesity, smoker, total cholesterol, HDL and triglycerides; HR 5 adjusted for sex, age, diabetes, hypertension, obesity, CRP, total cholesterol, HDL and triglycerides;

Table 5 Risk of mortality by ACR ≥2.7 and PAF for Tiwi people aged 18 years and over

	ACR <2.7		ACR ≥ 2.7				PAF(95%CI)**
	events	HR	events	Crude HR (95% CI)	HR1 (95% CI)	HR 2(95% CI)	
All natural death	34	1.0	169	5.9 (4.1-8.5)	4.3 (2.9-6.2)	3.3 (2.1-5.2)	0.66 (0.53-0.75)
Renal death*	0	1.0	70	See notes	See notes	See notes	1.00
Non-renal death	34	1.0	99	3.4 (2.3-5.1)	2.4 (1.6-3.5)	2.1 (1.3-3.4)	0.45 (0.26-0.60)
CVD death	18	1.0	42	2.7 (1.6-4.7)	2.0 (1.1-3.4)	1.7 (0.8-3.3)	0.34 (0.01-0.57)

*Notes: HR1 adjusted for sex and age; HR 2 adjusted for sex, age, diabetes, hypertension, obesity, total cholesterol, HDL and triglycerides; * HR of renal death for ACR≥ 2.7 vs.<2.7 could not be calculated because of no events in reference group; ** Population attributable fraction of death predicted by ACR ≥ 2.7mg/mmol & adjusted for age, sex and time of follow-up*

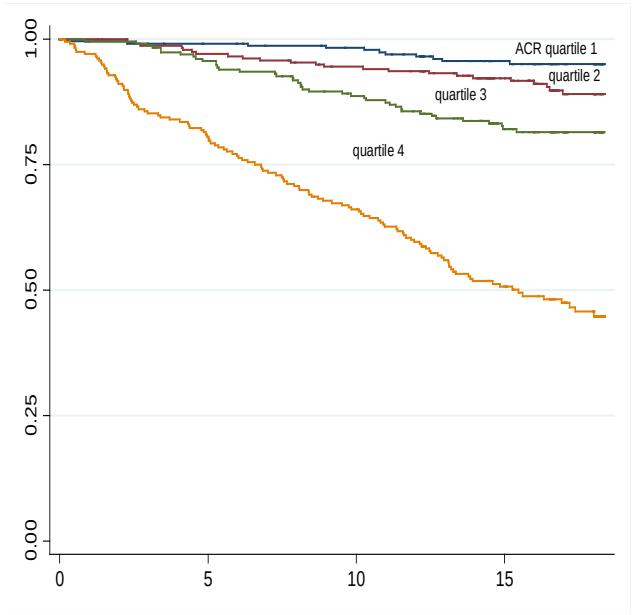

Figure 1A Survival of all natural death by baseline ACR quartiles.

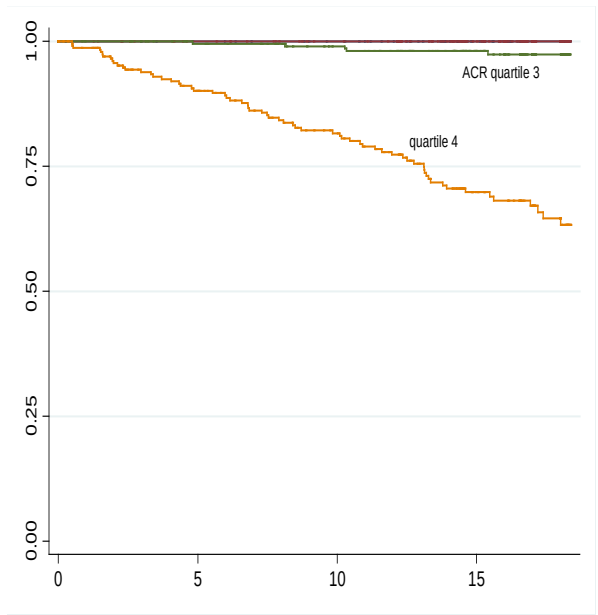

Figure 1B Survival of renal death by baseline ACR quartiles

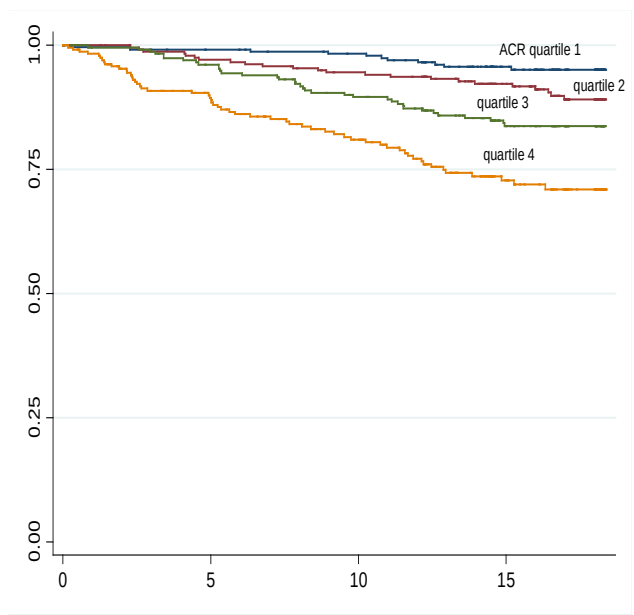

Figure 1C Survival of nonrenal death by baseline ACR quartiles

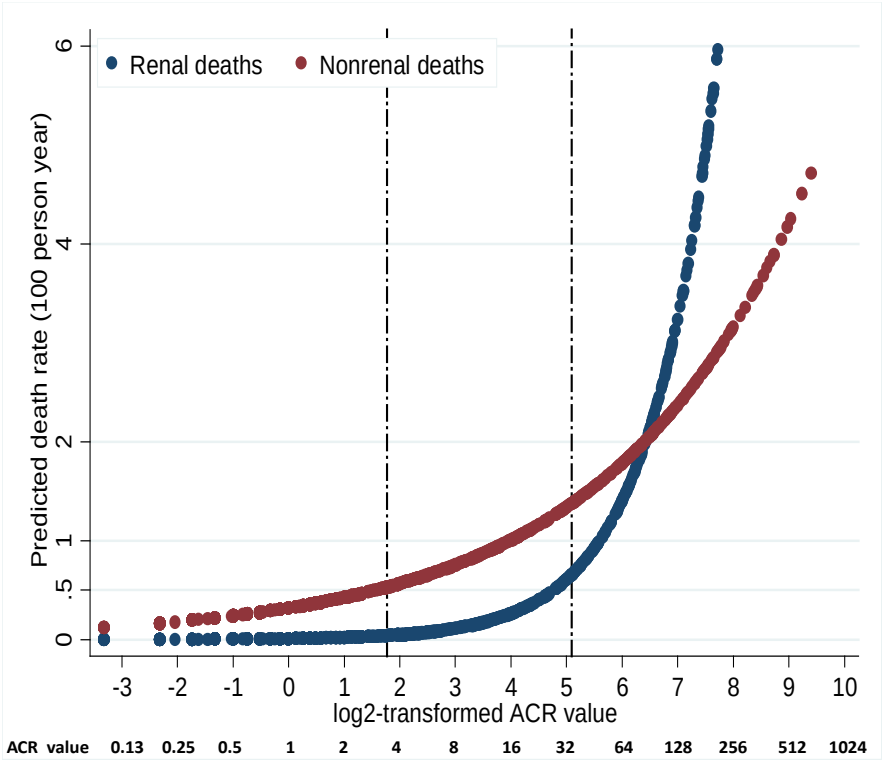

Figure 2 Predicted renal and nonrenal death rate (100 person years) by ACR

Notes: the two etched lines stand for actual ACR values= 3.4 and 34 mg/mmol, respectively;